REMARKS

Claims 1-27 are pending in the instant application. Claims 2-5, 9-24 and 26 have been withdrawn from consideration. Claims 1, 6-8, 25 and 27 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-16 of copending Application No. 10/311,108. Claims 1, 6-8, 25 and 27 further stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO01/96895 (Cook et al.) and further in view of WO00/40988 (Ardenkjær-Larsen et al.). Reconsideration is respectfully requested.

Claims 1, 6-8, 25 and 27 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-16 of copending Application No. 10/311,108. This rejection is respectfully traversed.

The Applicant respectfully submits that the two claimed inventions are patentably distinct and not obvious variants of each other. Claims 13-16 of US10/311,108 recite:

> **13. A method for investigating the state of a biological system containing at least one NMR active nucleus selected from 13C, 15N, 31P, 19F and/or 1H, said method comprising the steps of:**
> **hyperpolarising the NMR active nuclei in the system; and**
> **new line analysing one of the systems and samples extracted from the system by one of NMR spectroscopy and NMR imaging to generate an NMR pattern for the system.**
>
> **14. A method according to claim 13, further comprising the steps of:**
> **subjecting the system to a change in its state;**
> **hyperpolarising the NMR active nuclei;**
> **analysing the system or samples extracted from the system in its changed state by one of NMR spectroscopy and NMR imaging to generate an NMR pattern for the system in its changed state;**
> **comparing the NMR patterns for the system and the system in its changed state and identifying any changes in the NMR pattern.**

15. A method for investigating the state of a biological system containing at least one NMR active nucleus selected from 13C, 15N, 31P, 19F and/or 1H, said method comprising the steps of:
subjecting the system to a change in its state;
hyperpolarising the NMR nuclei;
analysing the system or samples extracted from the system by one of NMR spectroscopy and NMR imaging to generate an NMR pattern from the system;
comparing the pattern with a pattern obtained from a control system that was not subjected to a change in its state prior to hyperpolarisation and analysis; and
identifying any differences between the pattern from the test system and the pattern from the control system.

16. The method according to claim 15, wherein the test system is subjected to a change in its state by exposure to a drug.

Application no. 10/311,108 hence claims a method for investigating the state of a biological system containing a NMR active nuclei, the method including hyperpolarizing the nuclei, generating an NMR pattern, subjecting the system to a change by introducing a drug, hyperpolarizing the NMR active nuclei, generating a pattern for the system or samples after introducing drug and comparing the NMR patterns for the systems.

Conversely, the instant application claims a method for determining *in vivo* protein activity using MR detection to determine the influence of a drug on the activity of a protein. Further, by using more than one probe compounds, the activity of a family of proteins, e.g. a family of different isoenzymes, may be determined (page 5, lines 8-12). Application No. 10/311,108 is directed to the study of a test compound, e.g. (putative) drug, whose metabolism, distribution, excretion etc is monitored. There is no indication in the cited claims of a method for monitoring the effect of a putative drug on selected proteins or even family of proteins. Moreover, the reference claims fail to disclose, teach, or suggest, that the activity of a protein or family of proteins is monitored in its "changed and unchanged" state to determine whether a putative drug changes the activity of said protein or family of proteins. Furthermore, application no. 10/311,108 fails to disclose, teach, or suggest a method wherein at least two probe compounds enriched with ^{13}C or ^{15}N NMR active nuclei, is administered. Hence, the Applicant respectfully submits that the two inventions are patentably distinct. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1, 6-8, 25 and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO01/96895 (Cook et al.) and further in view of WO00/40988. The rejection is respectfully traversed.

The present invention, conversely, provides a more targeted approach to monitor the effect of a putative drug on selected proteins or even family of proteins. This is especially useful since proteins can be chosen which are known to play a certain role in the human or non-human body, e.g. metabolic enzyme families like CYP450 or transporter proteins (page 4, lines 3-10).

Cook et al. (WO 01/96895) discloses a method to use NMR for investigating the fate of a test compound, e.g. a drug which is administered to a biological system, e.g. a human. Hyperpolarisation of samples taken from the biological system leads to increased sensitivity of the NMR investigation. However, the method of Cook et al. does not determine protein activity of a protein or a family of proteins present in the biological system; it is the test compound, e.g. (putative) drug, which is studied and whose metabolism, distribution, excretion etc is monitored. Cook discloses, on page 13 and subsequently on pages 14-16, that an NMR pattern is generated from an NMR analysis of hyperpolarised samples taken from a biological system that has been subjected to a change in its state (e.g. by exposure to a drug) and that said NMR pattern is compared to another NMR pattern which was generated from an NMR analysis of the system in its unchanged state. It is however not disclosed by Cook et al. that the activity of a protein or family of proteins is monitored in its "changed and unchanged" state to determine whether a putative drug changes the activity of said protein or family of proteins. Cook simply discloses a very general method that fails to suggest all responses of a biological system to a drug that could be investigated. Further, Cook et al. is silent about selecting specific proteins targets and changing the state of a system by probe compounds which interact with the selected protein and a putative drug which may change the protein's activity.

Ardenkjær-Larsen et al (WO 00/40988) discloses NMR spectroscopic in vitro assays wherein the assay reagent is hyperpolarised. The assay reagent may be administered to a human or animal (page 17, lines 11-12) and NMR spectroscopic analysis may be performed of samples from said human or animal being. Ardenkjær-Larsen et al. further discloses that the assay may be a competition or binding assay wherein protein-protein interactions are studied (page 7). However, Ardenkjær-Larsen et al. is silent about using as an assay reagent probe compounds which interact with a certain protein or protein family and a putative drug and using the assay to determine the effect of the putative drug by comparing an NMR analysis of samples from a human or animal with and without the putative drug being present.

The present invention is directed to a method in which a mixture comprising at least two probe compounds, which all are enriched with ^{13}C-and/or ^{15}N NMR active nuclei and at least one putative drug, wherein the probe compounds are substrates, inhibitors or inducers of a protein, are used.

Cook et al. is silent about mixtures as claimed in claim 1. A test compound, e.g. a drug is used in the methods disclosed in Cook et al. and the fate of said drug is monitored by NMR.

Ardenkjær-Larsen et al. discloses a set of probe compounds (page 15, line 26) which may be used in an NMR method. However, no putative drug is present in said set of probe compounds, i.e. Ardenkjær-Larsen et al is silent about mixtures as claimed in claim 1.

Applicants respectfully submit that neither reference corrects the deficiencies of the other. Neither Cook et al. nor Ardenkjær-Larsen et al., or the combination of these, render the instant invention obvious. Applicant submits that claims 1 is thus patentably distinct over the cited references. Similarly, as claims 6, 7, 8, 25 and 27 depend from claim 1, the remaining claims are patentably distinct as well. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the remarks hereinabove, Applicant respectfully submits that the instant

application, including claims 1, 6, 7, 8, 25 and 27, is now in condition for allowance. Favorable action thereon is respectfully requested.

Any questions with respect to the foregoing may be directed to Applicants' undersigned counsel at the telephone number below.

Respectfully submitted,

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